Consideration of Chronic Disease Endpoints – The Options Report

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Approach to Setting DRI Values

• U-shaped curve for risk
  • Estimate Average Requirement (EAR)
  • Recommended Dietary Allowance (RDA)
  • Tolerable Upper Intake Level (UL)
EAR/RDA/UL approach

• Criteria:
  – “Essentiality” of the substance
  – Evidence of causality and dose response
  – Threshold for adequacy and adverse effects
  – Relevant population
  – Applicability of U-shaped risk curve

• These don’t always apply to food substance-chronic disease (CD) relationships
Addressing the challenges of using chronic disease endpoints to set DRIs
Options for Basing Dietary Reference Intakes (DRIs) on Chronic Disease Endpoints

- To critically evaluate key scientific issues involved in using chronic disease endpoints for setting DRIs
- To provide options for future decisions as to whether and/or how chronic disease endpoints can be incorporated into the setting of DRI values.
Key Questions

1. What are the evidentiary challenges important in selecting and using chronic disease endpoints in future DRI reviews?

2. What intake-response models can be considered for future DRI reviews when chronic disease endpoints are used?

3. What arguments can be made for and against continuing to include chronic disease endpoints in future DRI reviews?

What are the key scientific issues?
What are the options for addressing these issues?
What are the advantages and disadvantages of the various options?
Working Group Members

Diverse expertise – History of DRI work, DRI users, nutrition experts, epidemiologists, trialists, toxicologists, biostatisticians

- Chair: Cutberto Garza, M.D., Ph.D.
  - Jamy Ard, M.D.
- Stephanie Atkinson, Ph.D., F.C.A.H.S.
  - Dennis Bier, M.D.
  - Alicia Carriquiry, Ph.D.
  - Janet King, Ph.D.
- Daniel Krewski, Ph.D., M.Sc., M.H.A.
  - George Wells, Ph.D., M.Sc.
- William Harlan, M.D., F.A.C.P., F.A.C.P.M., F.A.F.M.
  - Dale Hattis, Ph.D.
  - Deborah O’Connor, Ph.D., R.D.
  - Ross L. Prentice, Ph.D.
  - Joseph V. Rodrigues, Ph.D.
Process

Pre-workshop

- Identify key issues that needed to be addressed and discussed at the workshop

Workshop
March 2015

- Review and discuss key issues related to the use of chronic disease endpoints in setting DRIs
- Identify potential options that could be used to set DRIs based on chronic disease endpoints

Post-workshop

- Develop options to address key issues related to the use of chronic disease endpoints in setting DRIs
- Publication of the Options Report including Strength and Weaknesses of Options
Important note

- This is not a consensus report and the options are not recommendations

- Options for addressing challenges are identified with strengths and weaknesses
Evidentiary challenges and options
Evidence for setting DRIs based on adequacy

- Establishing causality and/or dose response
  - RCT
  - Intervention trials
  - Metabolic/balance studies
  - Depletion/repletion
  - ≥3 doses (D-R)
Nature of the evidence differs for CDs

- Nutrient-Chronic Disease evidence mostly observational or associational
- Establishment of causality and/or dose response in absence of RCTs
- Inherent errors/bias associated with study type
  - Confounding and selection bias
  - Self-reported intake
Options for specifying an acceptable level of confidence and strength of the evidence

- Tools available for evaluating study quality and the strength of the totality of the evidence

- Options include:
  - Level of confidence specified that must be met before a DRI can be set
    - Eg. High vs moderate vs piece-together
  - Specify the level of certainty of the evidence used to set the DRI
    - Base values on available evidence and provide an evidence “grade”
Biomarkers should be on causal pathway

- Direct observations of disease endpoint due to low (EAR/RDA) or high (UL) intake of nutrient
- Indicators of status on the causal pathway for diseases of deficiency
  - Serum folate, serum 25(OH)D, serum ferritin
- Higher level of certainty of relationship
Biomarkers should be on causal pathway

- Food substance-CD often associated by surrogate or intermediate outcomes
  - Higher uncertainty
- Validated biomarkers (including intake) are few

Options for selecting biomarkers

- Options for determining causality and/or intake-response:
  - Only CD outcome or qualified surrogate disease marker
  - Also include non-qualified disease markers
  - Integration of multiple markers for a disease

- Options for intake assessment:
  - Use qualified biomarkers of intake (when available)
  - Also include non-qualified biomarkers of intake
Intake-response challenges and options
**EAR assumes a threshold for adequacy**

- **Threshold effect/Inflection point** between inadequate and adequate intakes
**UL assumes a threshold for upper intake**

- Highest average daily intake level likely to pose no risk of adverse health effects for nearly all people
- Assumes an inflection point
  - Intakes above the UL increases the risk of adverse effects
Absence of an inflection point

- Food substance-CD relationships can lack an inflection point
  - Eg. Saturated fats and LDL cholesterol
  - Also no “benefit”: Keep intakes as low as possible while consuming a nutritionally adequate diet
Absolute risk that affects all persons, all life-stage groups

At low and high intakes, there is 0 or 100% risk of deficiency or adverse effects
Risk is *absolute* and effects *all persons, all life-stage groups*

Example: Vitamin D and bone health

IOM, 2010
Relative risk that may not affect all persons, all life-stage groups

- Chronic Disease: Not all persons, not all life-stage groups
  - Often significantly <50% of population affected by the CD

Prevalence of diagnosed diabetes, Canada, 1998-2008

Source: Diabetes in Canada 2011, Figure 1-4
(data from chronic disease surveillance system)

http://www.med.uottawa.ca/sim/data/Diabetes_e.htm
Relative risk of chronic disease

- No one in a population is at 0 or 100% risk—they are at higher or lower risk compared to a baseline risk.
- Intake of food substances often alter disease risk by small amount (e.g. <10%).
Relative risk: Fibre and coronary heart disease

Greatest effect often at tail(s) of intake distribution – highest or lowest intakes have largest effect
Fibre AI based on median intake to achieve lowest relative CHD risk
Options for types of DRI values based on CD endpoints

- **CD risk reduction value**
  - Single value based on relative disease risk reduction
  - Family of targeted relative risk reduction values
  - Multiple values based on relationship with multiple CDs

- **Range of beneficial intakes**

- **ULs based on chronic disease endpoints**
  - Do not base ULs on CD endpoints
  - Threshold approach using relative disease risk ($UL_{CD}$)
  - Family of $UL_{CD}$ targeted risk reduction values
U-shaped risk model assumes interval between beneficial and harmful intakes
Overlap of benefit and harm

A food substance can be related to multiple chronic diseases with different risk relationship shapes.

Options: - “beneficial” DRI value not set higher than the lowest adverse effect
- set criteria for CD severity, prevalence, risk change required to set a value
- describe the nature of the evidence, benefits and risks
In summary...

- The DRI approach works well for estimating adequate intakes for essential nutrients
- The approach has not worked well when using chronic disease endpoints

- The Options Report provides a foundation for your work developing guiding principles for basing DRIs on chronic disease endpoints...

*We look forward to seeing the fruits of your labor!*